PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P26531A/CMU/MCM	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/04128	International filing date *(day/month/year)* 19.09.2003	Priority date *(day/month/year)* 19.09.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/66		
Applicant THE UNIVERSTITY OF ULSTE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.04.2004	08.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Jenkins, G Telephone No. +31 70 340-2608

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/04128

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-19 as originally filed

Claims, Numbers

1-11 received on 11.10.2004 with letter of 11.10.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 12-14
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The following document D1 is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: MCKILLOP ET AL: 'Production and characterization of specific antibodies for evaluation of glycated insulin in plasma and biological tissues.', J ENDOCRINOL, October 2001, vol. 167, no. 1, pages 153 to 163.

2 NOVELTY

2.1 The subject-matter of claims 1-11 is new in the sense of Article 33(2) PCT, since the prior art does not disclose using glycated insulin as a biomarker for: monitoring progression of diabetes towards an increased severity, prediction of individuals at risk of developing diabetes, or diagnosing the early onset of diabetes when glucose levels are still within the normal range.

3 INVENTIVE STEP

3.1 The subject-matter of claims 1-11 is considered inventive under Article 33(3) PCT.

3.1.1 The subject-matter of claim 1 is considered inventive under Article 33(3) PCT. Here, D1 is considered the closest prior art. This document discloses (the references in parentheses referring to this document): glycated insulin as a biomarker of diabetes (figure 7).

3.1.2 The additional technical feature of claim 1 over D1 is that glycated insulin is measured at two time-points and compared.

3.1.3 The technical effect associated with this is that an increased severity can be diagnosed if the concentration of glycated insulin is less at the second time-

point.

3.1.4 The problem to be solved by the present invention may therefore be regarded as the provision of a method for monitoring progression of diabetes towards an increased severity.

3.1.5 The solution to this problem is to measure and compare glycated insulin levels at two different time-points.

3.1.6 The solution to the problem is not suggested or derivable in an obvious way from the prior art. Indeed, the finding that glycated insulin levels decrease with increased severity of diabetes is completely the opposite to what would be expected from the disclosure of D1. Therefore, the subject-matter of claim 1 is inventive in the sense of Article 33(3) PCT.

3.2 The subject-matter of independent claims 2 and 3 is also considered inventive (Article 33(3) PCT), since it is additionally shown that glycated insulin levels are higher in people who are either at risk of diabetes or in the early stages of the disease when plasma glucose levels are still normal. This finding is surprising and unexpected, since previously it would have been assumed from the disclosure of D1 that glycated insulin levels would closely correlate with plasma glucose levels, which indicate the presence of diabetes. Since the subject-matter of claims 4-11 also contains this special technical feature, their subject-matter is likewise considered inventive (Article 33(3) PCT).

4 INDUSTRIAL APPLICABILITY

4.1 The subject-matter of claims 1-11 is industrially applicable in the field of *in vitro* diagnosis of diabetes and the distinguishing of the different disease stages thereof (Article 33(4) PCT).

Claims

1. A method of monitoring the progression of diabetes from a first timepoint to a later timepoint, said method comprising the steps
providing a first biological sample obtained at the first timepoint,
measuring the concentration of glycated insulin in said biological sample,
providing a second biological sample obtained at the later timepoint,
measuring the concentration of glycated insulin in said second biological sample,
determining the difference in concentration of glycated insulin between the first and second biological samples,
wherein a lower concentration at the second timepoint is indicative of increased disease severity and/or loss of control of blood glucose.

2. A method of early diagnosis of diabetes in an individual, the method comprising the steps
providing a biological sample in which glucose levels are within a normal range from said individual,
measuring the concentration of glycated insulin in the biological sample,
wherein the presence of glycated insulin at a concentration greater than a predetermined minimum is indicative of the presence of diabetes.

3. A method of predicting the onset of diabetes in an individual, the method including the steps of;
providing a biological sample from said individual,
measuring the concentration of glycated insulin in the biological sample,
wherein the presence of glycated insulin at a concentration greater than a predetermined minimum is indicative of predisposition to diabetes.

4. The method according to claim 3, wherein the concentration of glucose in the biological sample is within the normal range.

5. The method according to claim 2 or claim 4 wherein the normal range of glucose is less than 11.1 mmol/l in a random plasma sample.

6. The method according to any one of claims 2 to 5 wherein said predetermined minimum concentration is the concentration of glycated insulin measured in a sample from the same individual at an earlier timepoint.

7. The method according to any one of claims 2 to 6, wherein said predetermined minimum concentration of glycated insulin in a non fasted sample is at least 20 pmol/l.

8. A method as claimed in any preceding claim wherein glycated insulin in the sample is measured by means of radioimmunoassay (RIA).

9. Use of glycated insulin, as a predictive marker for glucose intolerance and/or diabetes.

10. Use of glycated insulin as a predictive marker for prediabetes or to predict the onset of diabetes.

11. An *in vitro* assay method for detecting diabetes or the predisposition to diabetes by determining the presence of glycated insulin in a biological sample, in which glucose levels are normal, said assay method comprising the steps:
providing a biological sample;
determining whether the concentration of glycated insulin in the biological sample is at least 20 pmol/l;
wherein the presence of glycated insulin at a concentration greater than 20 pmol/l is indicative of diabetes or predisposition to diabetes.